P-94/989

National Cancer Institute

Cancer of the Prostate

Research Report

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

HE 20.3166

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The production of National Cancer Institute publications is supported in part by contributions to the National Cancer Institute Gift Fund, Box P, 9000 Rockville Pike, Bethesda, Maryland 20892.

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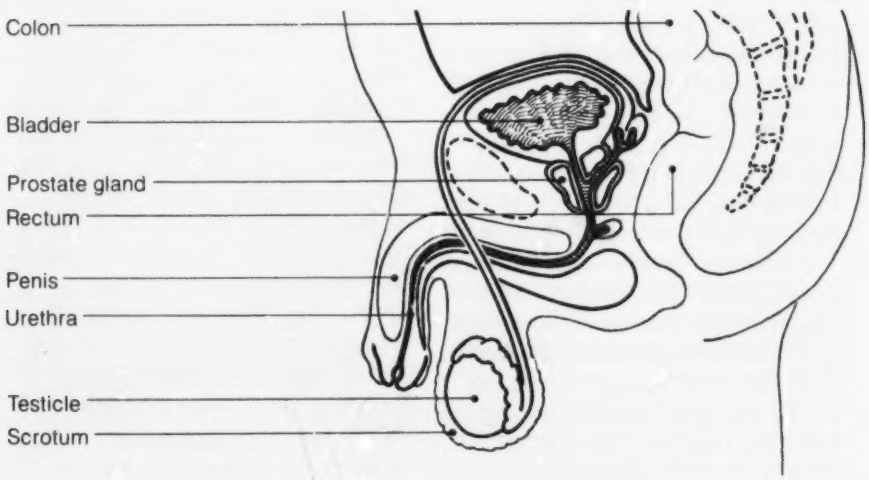
This publication describes current knowledge of the incidence, possible causes, detection and diagnosis, and treatment of prostate cancer. The information presented here was gathered from medical textbooks, recent articles in the scientific literature, National Cancer Institute (NCI) researchers and other scientists, and the NCI's PDQ (Physician Data Query) database. This Report expands upon the NCI pamphlet *What You Need To Know About Prostate Cancer.*

Knowledge about cancer of the prostate is increasing steadily. Up-to-date information on this and other cancer-related subjects is available from the toll-free Cancer Information Service at 1-800-4-CANCER.

Description and Function of the Prostate

The prostate gland and the testes are part of the male reproductive system. The prostate is located inside the body at the base of the penis, just below the bladder and in front of the rectum. It is composed of glandular and fibrous tissue enclosed in a capsule of connective tissue. The prostate surrounds the first inch or so of the urethra, the canal that carries urine from the bladder. Normally, it is about 1½ inches in diameter and about ¾ of an inch thick.



Normal activities of the prostate depend on the presence of the male hormone testosterone, which is manufactured by the testes. The prostate produces semen, the thick, whitish fluid that carries sperm. Other functions of the prostate are not well understood.

Benign Conditions

Like all other tissues and organs of the body, the prostate gland is composed of individual cells. Normally, cells divide and reproduce in an orderly, well-controlled manner to replace worn-out and injured tissue. Sometimes, however, cell division becomes excessive, leading to an overgrowth of tissue. When the overgrowth causes enlargement of the prostate gland, the condition is known as benign prostatic hyperplasia (BPH). Enlargement of the prostate is common in older men; it is estimated that more than half of men in the United States above the age of 40 have an enlarged prostate gland.

Sometimes excessive cell division results in the formation of tumors. These tumors may be benign (noncancerous) or malignant (cancerous). Both BPH and benign tumors can crowd and press on adjacent organs and may interfere with normal urinary function. However, neither invades neighboring tissue, and neither spreads to other parts of the body. It is rare that either is life-threatening.

Prostate Cancer

By contrast, cancerous growths not only compress but also invade and destroy normal tissue. In addition, cancer cells can break away from the primary tumor in the prostate and spread, or metastasize, through the blood and lymph systems to other parts of the body, where they form secondary (metastatic) tumors. When prostate cancer spreads, it most commonly affects the lymph nodes, bladder, rectum, lungs, liver, and especially the bones—most often the pelvic bone and lower spine. Microscopically, the cancer cells of these secondary tumors are identical to those of the primary cancer. As such, they retain many of the characteristics of the original prostate cancer despite being located in the bone, lung, liver, or elsewhere. These secondary tumors are referred to as "metastatic prostate cancer" (rather than bone, lung, or liver cancer) to indicate that they are all part of a single disease and are not new cancers originating in these organs. Treatment for cancer that has spread must take into account the site and type of the primary tumor as well as the location and extent of the metastatic tumors and other factors.

Prostate cancer most often arises from deep within the prostate gland not in the benign prostatic hypertrophy cells so common in older men. Over 95 percent of prostate cancers are adenocarcinomas. When viewed under a microscope, the cells in adenocarcinomas grow in patterns that have a gland-like appearance. The remaining prostate cancers are atypical adenocarcinomas, sarcomas, peripheral ductal carcinomas, adenoid cystic carcinomas, endometrioid tumors, carcinosarcomas, and malignant lymphomas. These unusual cancers are not discussed in this Research Report.

Incidence and Mortality

Cancer of the prostate is one of the most common forms of cancer among American males. In the United States, approximately 1 man in 11 will develop prostate cancer during his lifetime. Found primarily in men over the age of 50, prostate cancer becomes increasingly common with each decade of life. About 80 percent of cases are diagnosed in men over 65.

The age-adjusted incidence of prostate cancer increased consistently from 45.3 to 76.4 per 100,000 from 1950 to 1985. During that period, the overall increase was 67 percent, or about a 1.8 percent increase each year. It is estimated that 99,000 new cases of prostate cancer were diagnosed in the United States in 1988. The increase in incidence is believed to be largely (but not exclusively) due to improved detection of the disease.

The true prevalence of prostate cancer (the total number of cases at a particular time) may be higher than available statistics indicate, especially in men over the age of 70. Autopsy examinations of elderly men who die from other causes often reveal previously undiagnosed cancer of the prostate. In addition, unsuspected prostate cancer is often diagnosed during microscopic examination of prostate tissue removed during surgery for other diseases of the prostate. It is not clear what the natural rate of progression would be for these early cancers, but epidemiologic studies have shown that men who have prostate cancer incidentally discovered during examination for other reasons have survival patterns similar to those of age-matched members of the general population.

Although the incidence of new cases of prostate cancer has increased steadily over the past 35 years, the mortality rate has

increased only slightly. Prostate cancer was responsible for about 28,000 deaths during 1988. The 5-year survival rate for all stages of prostate cancer has improved from 43 percent in 1950 to 73 percent in 1980, due to better understanding of the epidemiology of this disease, more effective screening and detection techniques, and improved treatment.

Black men in the United States have the highest incidence rate of prostate cancer in the world. Although reliable data on black Africans are not readily available, their prostate cancer rates appear to be much lower than those for American blacks. The reasons for this apparent difference are not known. However, it appears that socioeconomic and lifestyle factors, rather than an inherent racial predisposition, explain the difference. Limited access to health care and detection of prostate cancer only after it has produced symptoms and is in an advanced stage contribute to the poor survival from prostate cancer among American black men.

The incidence of prostate cancer varies among population groups and by geographic area. This cancer is common in Western Europe and North America, but rare in the Near East, in some parts of Africa, and in Central and South America.

Possible Causes

Little is known about the causes of prostate cancer, and it is seldom possible to explain why a man develops this disease. Scientists believe that cancer of the prostate develops over a period of many years as a result of gradual changes in the cells. No single theory explains the development of this disease, but a number of possible causes have been suggested. Investigations have focused on four general areas: genetic predisposition (heredity), hormonal influences, environmental and lifestyle factors, and sexually transmitted agents.

The data from population studies have produced conflicting results. Some studies suggest a genetic predisposition to prostate cancer and an increased risk for blood relatives of men with the disease. However, other studies have not confirmed a genetic link, and data from studies of people migrating from one geographic area to another point to the importance of environmental factors, including diet, in the development of prostate cancer. Epidemiologic studies suggest that a diet rich in fat may increase the risk of prostate cancer. For example, Japanese

in Hawaii have more fat in their diet and a higher incidence of prostate cancer than do their counterparts in Japan. In addition, prostate cancer has been linked with the consumption of animal fat and protein among several other ethnic groups in Hawaii.

Scientists have long suspected that hormones contribute to the development of prostate cancer. When the testicles are removed before puberty, there is little risk that a man will develop this disease, apparently because the primary source of male hormones has been removed. Moreover, researchers can induce prostate cancer in rats by prolonged administration of hormones. However, the precise role of hormones in the development of prostate cancer in humans has been difficult to determine. Currently, scientists are comparing the testosterone production and metabolism in prostate cancer patients and their brothers as well as in men from families who do not have prostate cancer. These studies are designed to learn whether these processes are different in families whose members do not have prostate cancer.

Prolonged workplace exposure to cadmium, a metallic element used during welding, electroplating, and the production of alkaline batteries, may increase the risk of prostate cancer. But dietary exposure to cadmium (from oysters, for example) does not have the same effect. Workers in the rubber industry may also be at increased risk. However, the results of these studies are not conclusive.

The possible role of sexually transmitted viral diseases in the development of prostate cancer has been examined by a number of researchers. The work is continuing, but currently there is no firm evidence to link sexually transmitted diseases and prostate cancer. New technology is enabling scientists to further explore the possibility of a viral etiology.

Some investigators have suggested a relationship between BPH and prostate cancer, but studies have produced conflicting results. While one large study indicated that men with BPH are at higher risk for prostate cancer, another found no increased risk associated with this condition.

Detection

Since the causes of prostate cancer remain unknown, prevention of the disease is not yet possible. However, when the disease is detected early, more men can be treated successfully. Based on scientific information currently available, the National Cancer Institute has suggested guidelines for the early detection of prostate cancer. They should be considered along with a person's medical history.

Early Detection

The NCI guidelines for early detection of cancer encourage an annual digital rectal examination of the prostate for all men beginning at age 40. At present, this is the most effective way to detect the disease at an early, more curable stage. The location of the prostate in front of the rectum allows the physician to feel irregularities or unusually firm areas. The rectal exam can reveal a cancerous growth before symptoms develop. This examination is also important for early detection of rectal cancer. Some doctors have suggested the use of transrectal ultrasound (see page 8 & 9) to screen (detect the disease in men without symptoms) for prostate cancer. Thus far, the value of transrectal ultrasound for this purpose has not been proven.

Symptoms

Most often, there are no symptoms in the early stages of prostate cancer. When symptoms do occur, they depend on the size and location of the growth.

Symptoms that should cause a man to consult a doctor include weak or interrupted urine flow, frequent urination (especially at night), inability to urinate or difficulty in starting urination, blood in the urine, or painful or burning urination. Persistent pain in the back, hips, and pelvis may suggest prostate cancer even when other symptoms are absent.

These problems can be caused by a variety of conditions and diseases, including infections, BPH, and prostate cancer. It is not possible to diagnose cancer from the symptoms alone, so any persistent urinary problems or pain should be evaluated promptly by a physician. A man who is experiencing urinary symptoms may wish to be evaluated by his family doctor or be referred to a urologist, a doctor who specializes in diseases of the urinary and male reproductive systems.

Diagnosis

To determine the cause of any of these symptoms, the doctor begins by taking a careful medical history, performing a thorough physical exam (including a digital rectal examination), and ordering laboratory tests.

Enlargement of the gland and/or the presence of firm or irregular areas in the prostate gland indicate a need for additional tests. These tests usually include urinalysis, blood studies, and x-rays, such as an intravenous pyelogram (IVP). The IVP is a series of x-rays taken after a substance is injected that outlines the kidneys, ureters, and bladder. It can reveal obstructions or abnormalities in these organs and help the doctor determine whether the symptoms are caused by a problem in the prostate or in the urinary tract.

If the doctor suspects prostate cancer, the patient is usually referred to a specialist (such as a urologist or surgeon) for a biopsy, which is the only way to make a definite diagnosis. A small tissue sample is removed for microscopic examination by a pathologist (a doctor who specializes in the diagnosis of disease by studying cells and tissues removed from the body).

In the United States, core needle biopsy and fine needle aspiration biopsy are the two most common biopsy methods. The method chosen for a particular patient depends on his physical condition, the apparent extent of the tumor, and other factors. In core needle biopsy, a tissue sample is removed with a special needle inserted by a transperineal (through the area between the scrotum and the anus) or transrectal (through the rectum) route. It can be performed as an outpatient procedure, but may require a local or general anesthetic. In fine needle aspiration, a special needle is inserted into the prostate through the rectum, and a cell sample is withdrawn. This procedure is performed on an outpatient basis, generally without anesthesia. It is becoming an increasingly common biopsy procedure as more physicians are trained and become experienced in carrying it out and as pathologists develop expertise in its interpretation.

Staging

If the biopsy confirms prostate cancer, the patient may benefit from a review of his case by a medical team composed of a variety of health professionals. A team might include an oncologist (a cancer specialist) and/or a urologist, radiation therapist, nursing professionals, and rehabilitation specialists. The composition of the team will depend on the patient's needs and the staff of the hospital or treatment center.

The physician conducts additional tests to establish the extent of the disease. This important step, called staging, helps in planning the most appropriate treatment for each patient. Staging procedures include a repeat of the rectal exam. The physician attempts to determine whether the tumor is contained within the gland or has spread beyond the prostate. The physician also feels the nearby lymph nodes for signs of enlargement, which may indicate the presence of cancer cells.

The spread of cancer cells to the lymph nodes is sometimes detectable with lymphography (x-rays taken after a substance is injected that outlines the lymphatic system). However, the most precise way to determine whether cancer is present in lymph nodes is by surgical removal and microscopic examination of the nodes. This is a major surgical procedure with some risk, however, and doctors are not in agreement about its usefulness for all prostate cancer patients.

Staging Techniques

To stage prostate cancer accurately, other techniques to produce images of the internal organs are used. These may include transrectal ultrasound, computed tomography (CT scan), and magnetic resonance imaging (MRI). While each of these tests may contribute valuable information, there is no single best procedure, and none is completely accurate.

Transrectal ultrasound uses sound waves produced by a probe inserted in the rectum. These sound waves bounce off the prostate and produce a pattern of echoes that a computer converts into a picture.

This procedure may improve staging by estimating the size of the primary tumor and identifying local spread, but it cannot assess the size of the lymph nodes. This relatively new technique is not available at all treatment centers.

CT scans are a series of x-rays taken as an instrument called a scanner revolves around the patient. A computer receives the x-ray images and creates a cross-sectional picture of the area of the body being examined. While CT scans can detect enlarged nodes, the images they provide of the prostate area are poor.

An MRI scanner contains a powerful electromagnet that excites the hydrogen molecules in water, the main component of all soft tissue. The hydrogen molecules, in turn, give off tiny electrical charges that are picked up by the scanner and transformed into an image of the tissue being examined. MRI provides good images of the prostate and does not involve radiation. It is comparable to the CT scan in detecting enlarged lymph nodes. Currently, however, the cost of MRI and its lack of widespread availability limit its application.

A bone scan can help the doctor determine whether the cancer has spread to the bone. The patient is given an intravenous injection of a mildly radioactive substance that collects in areas of active bone growth and gives off radiation. These radioactive areas are then pinpointed by a scanner and recorded on x-ray film. A bone scan detects bone abnormalities, but it does not always distinguish cancer from other problems such as arthritis, infections, or fractures.

Flow cytometry is a new laboratory procedure that is used to determine how fast a tumor is growing and to measure DNA, the genetic material in cells. This test identifies the cell characteristics that appear to correlate with the aggressiveness (growth rate and potential to metastasize) of the cancer. Research is under way to evaluate how useful flow cytometry will be in planning treatment for prostate cancer patients.

Staging Systems

Several staging systems have been used for prostate cancer. The widely used American Urologic System divides prostate cancer into stages A, B, C, and D.

Stage A: Microscopic clusters of cancer cells are found in tissue samples removed during surgical treatment for benign disease; stage A disease cannot be detected by the physician during rectal examination.

A1: The tumor cells are well differentiated and are found only in one area of the gland.

A2: The tumor cells are poorly differentiated or occur in many areas of the gland.

Stage B: Cancer is confined within the capsule of the prostate; it can be felt by the physician during rectal examination.

B1: A single tumor is found in one lobe of the prostate.

B2: The cancer is more extensive, involving one or both lobes.

Stage C: The cancer extends outside the prostatic capsule to nearby tissues or organs.

Stage D: The cancer has spread to regional lymph nodes or beyond the pelvis to the bone or other organs.

D1: Only regional lymph nodes are involved.

D2: The cancer has spread to the bone, distant lymph nodes, or other distant organs.

Another important part of pretreatment evaluation is determining the grade, or degree of differentiation, of the cancer cells. Grading is an effort to predict the aggressiveness of a tumor based on the microscopic appearance of the cancer cells. Well-differentiated cancer cells resemble their normal counterparts, while poorly differentiated cancer cells are disorganized and abnormal looking. Since poorly differentiated cells tend to spread more rapidly than well-differentiated ones, this characteristic helps the physician make recommendations about treatment.

The widely known Gleason grading system is one of a number of different grading strategies that classify cancer cells based on their microscopic appearance. Lower Gleason scores (1 through 4) indicate well-differentiated cells. Intermediate scores (5 through 7) denote tumors with moderately differentiated cells. Higher scores (8 through 10) describe poorly differentiated cells.

Tumor Markers

Additional laboratory tests, including identification of substances known as tumor markers, can help define the extent of the cancer. Tumor markers are substances detectable in the blood or urine that suggest the presence of cancer. One of these is prostatic acid phosphatase (PAP), an enzyme found in the blood. A certain amount of this enzyme is normally secreted by the prostate after puberty. In many men with prostate cancer, the enzyme level rises above normal when tumor tissue extends beyond the capsule of the prostate. Thus, PAP determinations may help to identify patients with metastatic disease. However, this test is not entirely reliable because elevated PAP levels may be observed in men with noncancerous diseases and do not always occur in those with prostate cancer.

The serum prostate-specific antigen (PSA) is another tumor marker. This protein is produced by the cells in normal, benign hyperplastic, and malignant prostate tissue. The level of PSA in the blood goes up in men with prostate cancer and other diseases of the prostate. According to recent research, this marker may be more reliable than prostatic acid phosphatase. Thus far, no large-scale studies have evaluated PSA, but it seems likely that PSA and PAP will be used together to help stage prostate cancer as well as to assess the patient's response to treatment.

Treatment

The outlook for patients with prostate cancer has improved steadily since 1950. While the incidence of the disease has been increasing, mortality rates have remained relatively constant. This pattern can probably be explained by a combination of factors: more frequent diagnosis of very early cancers, diagnosis at earlier stages of disease, and improvements in treatment.

Although the growth rate of prostate cancer varies somewhat unpredictably from case to case, doctors generally recommend therapy based on the stage of the disease and certain characteristics of the cells. They also take into account the patient's age and medical history, as well as the probable risks and benefits of the treatment.

Prostate Cancer Therapies

Surgery is used to treat both benign prostate enlargement and prostate cancer. Transurethral resection of the prostate (TUR or TURP) is the most common procedure used to relieve urinary obstruction when the gland is slightly or moderately enlarged. This technique may also be used to remove small cancers. During TURP, an instrument inserted through the penis trims away excess prostate tissue. Tissue removed during surgery is examined by a pathologist.

Radical prostatectomy is a more extensive procedure. It involves the removal of the entire prostate gland and surrounding tissues. Surgeons use several different techniques to remove the prostate gland. In retropubic prostatectomy, an incision is made from the navel to the pubic bone to permit removal of the prostate and pelvic lymph nodes. In perineal surgery, the incision is made between the scrotum and the anus. The perineal approach requires less operating time, but it does not give the surgeon access to the pelvic lymph nodes. In patients with medical conditions such as heart or lung disorders, the perineal technique may be safer. If necessary, lymph nodes can be removed during another procedure.

In the past, impotence was a side effect for nearly all patients undergoing radical prostatectomy. However, improved surgical techniques can often spare potency by bypassing the nerves necessary for erection. This procedure is being

widely adopted, but doctors agree that attempts to preserve potency are secondary and that complete removal of the tumor is most important. Urinary incontinence and stricture (narrowing of the urethra) are two other possible side effects of radical prostatectomy, but they are not common.

Radiation therapy, the application of high-energy rays to destroy cancerous tissue, has been used to treat prostate cancer since the early 1900s. While early efforts were limited by radiation damage to normal tissues, advances in technology have given radiation therapy an important role in the treatment of this disease. The radiation may be delivered by machine (external beam radiation) or may come from radioactive material implanted in the body (interstitial radiation therapy).

External beam radiation can be sharply focused on localized tumors, sparing normal tissues in the area. Usually, treatment is administered over 6 to 7 weeks. When used to treat a wider area to which cancer cells may have spread, such as the pelvic lymph nodes, the treatment is called "extended field radiation."

Radiation therapy commonly produces certain side effects, including inflammation of the bladder and bowel. These problems are managed with medication and are usually temporary. Some patients experience a gradual loss of sexual potency following treatment. Side effects of radiation therapy can be minimized with careful treatment planning and the use of sophisticated radiation techniques, including linear accelerators, which produce high-energy x-ray beams.

Interstitial irradiation, also called brachytherapy, may be used alone or along with external beam radiation. The treatment involves temporary implantation of the radioactive isotopes of gold (Au198), iodine (I125), or iridium (Ir192) directly into a tumor. Used alone, interstitial irradiation affects only the prostate gland and the immediate area around it. The side effects of radiation implants vary with the isotope chosen. Not every patient experiences side effects. Some men have temporary urinary tract symptoms, and a small number become incontinent. While sexual potency may be decreased somewhat, most men are able to have sexual intercourse.

Hormone therapy is the standard treatment when prostate cancer has spread to distant parts of the body, when the disease recurs, or, in some cases, when the tumor is locally advanced. For years, scientists have known that prostate cancer cells depend on male sex hormones known as androgens for their growth. The purpose of hormone therapy is to deprive the tumor of the predominant circulating male hormone, called testosterone. While hormone therapy is not a cure, it usually arrests the disease for prolonged periods and often relieves pain and other symptoms caused by the cancer.

Doctors use a number of different hormone therapies to prevent the action of male hormones on the prostate gland. Surgical removal of the testes, an operation called orchiectomy, is the oldest and most widely used form of hormone therapy. This procedure, which is a low-risk operation, eliminates the major source of testosterone. However, some patients and doctors find this procedure psychologically unacceptable, as it causes a loss of libido (sex drive) and impotence. In addition, a small number of patients have hot flashes.

Another hormone approach is the administration of estrogen, a female hormone that reduces or eliminates the body's production of testosterone. Diethylstilbestrol (DES) is a synthetic estrogen frequently prescribed to treat advanced or recurrent prostate cancer.

As with most types of hormone therapy, estrogen administration has some undesirable side effects. Long-term effects may include loss of libido, impotence, and breast enlargement or tenderness. Radiation to the breasts prior to estrogen treatment can prevent this problem, but it appears that radiation therapy is ineffective once breast enlargement has occurred. Administration of high doses of estrogen is also known to increase the risk of heart and circulatory disorders in men. However, studies indicate that reducing the diethylstilbestrol dose to 1 milligram (mg) per day lowers the risk of cardiovascular effects while maintaining the effectiveness of the treatment.

Most studies report no added benefit from combining orchiectomy

with estrogen therapy. Use of one or the other, though, helps about 70 percent of patients, with benefits sometimes lasting several years.

Another approach to reducing testosterone levels is the use of LHRH agonists. LHRH (luteinizing hormone-releasing hormone) is a hormone that controls the production of sex hormones in men and women. (Scientists also refer to it as gonadotropin-releasing hormone.) Agonists of LHRH—compounds that are structurally similar to LHRH—are given in large doses on a long-term basis to suppress the production of testosterone. LHRH agonists are apparently as effective as estrogen therapy or orchiectomy in reducing the level of testosterone in the body.

Leuprolide (Lupron), an LHRH agonist, was approved in 1985 by the U.S. Food and Drug Administration (FDA) as a form of hormone treatment for advanced prostate cancer. Currently, this treatment is given by daily injection. As with other treatments that suppress testosterone, impotence is common, and patients often experience hot flashes. Also, leuprolide may temporarily stimulate tumor growth and symptoms, a phenomenon known as "tumor flare," which may limit its usefulness in some patients.

Other LHRH agonists being tested include Buserelin, Zoladex, Nafareline, and D-Trp-6-LHRH. These drugs are administered by nasal spray or by injection; the injection method is preferred because the drug is better absorbed. Recently, researchers have been experimenting with a new method of administration for these drugs and for leuprolide. A pellet of the drug, called a depot, is injected beneath the skin of the abdomen, and the drug is slowly released over a period of 1 to 3 months. The FDA has not yet approved this method for general use.

Antiandrogen compounds are another type of hormone treatment. They function by inhibiting the action of testosterone on the prostate. Antiandrogens can be divided into two types: steroidal agents and nonsteroidal agents. Megestrol acetate (Megace), cyproterone acetate, and medroxyprogesterone acetate (Depo-Provera and several other brands) are examples of progestational agents (steroids) that function as antiandrogens. The activity of these steroidal agents varies, and their usefulness can be limited by their tendency to lose effectiveness

with long-term administration. Few significant side effects have been noted with this treatment. Non-steroidal agents include Anadron (RU 23908) and flutamide.

Research has shown that a combination of LHRH agonists and flutamide can block the small amount of androgens produced by the adrenal glands and improve response to hormone therapy. In 1989, the FDA approved the use of flutamide (Eulexin) in combination with leuprolide for the treatment of advanced prostate cancer. The FDA's approval was based on the results of recent clinical trials. In an NCI-sponsored trial carried out at five medical centers, patients treated with the combination of leuprolide and flutamide have survived for an average of about 7 months longer than those who received leuprolide alone. Moreover, the combined therapy has been well-tolerated by patients and was effective in relieving pain. NCI scientists are continuing to monitor the patients participating in this study. Their records will be reviewed regularly to evaluate the effectiveness of the combined therapy.

Chemotherapy (treatment with anticancer drugs) may benefit patients who have relapsed after hormone therapy. In such cases, efforts to control the disease with additional hormonal approaches are usually not successful, probably because of the presence of cancer cells that do not depend on hormones to grow. Doctors are studying the value of various anticancer drugs used individually and in combination. They are also investigating the timing of therapy for the best effect and the possibility of combining chemotherapy with hormone therapy.

Biological therapy, also known as biotherapy or immunotherapy, is the use of biological agents to fight cancer. It is a new form of cancer treatment based on the knowledge and tools of modern molecular biology, immunology, and genetics. Biological therapy works either directly against the cancer or indirectly to modify the relationship between the tumor and the patient. It may enhance a cancer patient's immune system so that the system will fight the growth of

cancer cells, eliminate or suppress body responses that permit cancer growth, or make a cancer cell more sensitive to destruction by the patient's immune system. Interferons, interleukin-2 (IL-2), tumor necrosis factor, interferon inducers, monoclonal antibodies, differentiation agents, and adoptive cellular therapy with lymphokine-activated killer (LAK) cells and interferon-activated macrophages are among the many approaches being tested in patients with cancer.

Treatment Planning

The choice of treatment depends on many factors. These will include the stage of the disease, the patient's age and other medical conditions, the anticipated side effects, the patient's ability to comply with treatment, and the preference of the patient and his doctor.

In addition to the therapies currently in general use, doctors are seeking new and better ways to treat prostate cancer. Treatments that have shown promise in the laboratory and in animal studies are evaluated in clinical trials with cancer patients. Clinical trials (investigational protocols) are designed to answer specific scientific questions and to determine whether a new treatment is safe and effective for patients. Many of the current standard treatments for cancer patients were developed in such clinical studies. Clinical trials are available for patients with all stages of prostate cancer. The NCI encourages patients and their doctors to consider this possibility when selecting treatment for prostate cancer. Information about how patients and their doctors can learn about current clinical trials is found on page 20.

Following is a general description of treatment options by stage of disease.

Stage A

Older patients diagnosed with stage A1 prostate cancer that was found during TURP for treatment of a noncancerous prostate condition usually require no further treatment. Generally, the patient is advised to return for regular examinations. Active treatment may be considered for stage A1 prostate cancer in younger men (ages 50–60).

Because patients diagnosed with stage A2 prostate cancer are at somewhat higher risk of having their disease spread, radiation therapy or surgical removal of the prostate may be recommended. The outlook for stage A1 patients is excellent; their survival usually equals that of the general population of the same age.

In investigational protocols for patients with stage A disease, researchers are trying to learn whether hormone therapy is useful in preventing the cancer from recurring.

Stage B

When prostate cancer has not spread beyond the capsule, the disease can be treated effectively with either radiation therapy or surgery (removal of the prostate and pelvic lymph nodes). Ten-year followup studies indicate that survival rates are about the same for patients treated by either external beam radiation or surgery. Because primary radiation therapy has not been in general use as long as prostatectomy, patients treated with radiation are still being followed to determine whether the similarity in survival persists after 15 years.

Clinical trials for patients with stage B disease include studies of new types of radiation therapy and drugs that may make prostate cancer cells more vulnerable to radiation treatment.

Stage C

Stage C prostate cancer is usually treated with external beam radiation therapy, but surgery or interstitial radiation may be recommended for some patients. Primary radiation treatment is delayed 4 to 6 weeks after TURP to reduce the risk that the urethra will close.

For patients who undergo radical prostatectomy, postoperative radiotherapy may be suggested if the tumor extends beyond the capsule of the prostate or if the seminal vesicles are involved. Radiotherapy may also be suggested for patients who have a detectable level of PSA more than 3 weeks after surgery. Further study is needed to clarify the value of postoperative radiotherapy.

Because hormone treatment has side effects, doctors usually do not recommend it for patients with stage C prostate cancer, and currently there is no evidence that survival time is improved by begin-

ning treatment before the patient experiences symptoms. However, some stage C patients do have urinary problems or other discomfort because of their disease. In these situations, the doctor may suggest radiation, TURP or other surgery, or hormone treatment to relieve symptoms.

For stage C patients, researchers are investigating new methods of radiation therapy combined with the use of hormones to control the growth of the cancer.

Stage D

Hormone therapy is the mainstay of treatment for patients with stage D prostate cancer. Although cure is seldom, if ever, possible, most patients respond quite favorably initially. When hormone therapy begins, most patients experience pain relief and prompt improvement of their other symptoms. Laboratory test results often return to normal, the primary tumor may shrink, and secondary tumors may decrease in size and number. Some physicians delay hormone therapy until symptoms (such as bone pain or bladder obstruction) occur, while others administer hormone therapy when the diagnosis of stage D, especially stage D2, cancer is made. TURP is sometimes done to relieve localized problems.

Investigational protocols for stage D patients include experimental forms of radiation therapy, combining chemotherapy with hormone therapy, single- and multiple-agent chemotherapy regimens, and biological therapies.

Recurrent Prostate Cancer

When patients receiving hormone therapy relapse, additional hormone therapy is usually prescribed. However, one study has reported that chemotherapy is superior to further hormonal approaches in such situations. Clinical trials investigating new hormonal and chemotherapeutic agents or biological treatments are often considered for patients with recurrent prostate cancer.

Clinical Trials and PDQ

To improve the outcome of treatment for patients with prostate cancer, the National Cancer Institute supports clinical trials at many hospitals throughout the United States. Patients who take part in this research make an important contribution to medical science and may have the first chance to benefit from improved treatment methods. Physicians are encouraged to inform their patients about the option of participating in such trials. To help patients and doctors learn about current trials, the NCI has developed PDQ (Physician Data Query), a database designed to give doctors quick and easy access to:

- descriptions of current clinical trials that are accepting patients, including information about the objectives of the study, medical eligibility requirements, details of the treatment program, and the names and addresses of physicians and facilities conducting the study;
- the latest treatment information for most types of cancer; and
- the names and addresses of physicians and organizations involved in cancer care.

To access PDQ, doctors may use an office computer with a telephone hookup and a PDQ access code, or the services of a medical library with online searching capability. Most Cancer Information Service offices (1–800–4–CANCER) provide physicians with free PDQ searches and can explain how to obtain regular access to the database.

Patients may ask their doctor to use PDQ or may call 1–800–4–CANCER themselves. Information specialists at this toll-free number use a variety of sources, including PDQ, to answer questions about cancer prevention, diagnosis, treatment, and research.

Selected References

The materials marked with an * are distributed free of charge by the NCI. Ordering information is provided on page 22. The other items are not available from the NCI; they can be found in medical libraries, many college and university libraries, and some public libraries.

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Additional Information

For additional information on this subject and for other NCI publications, write to the Office of Cancer Communications, National Cancer Institute, Bethesda, Maryland 20892, or call the Cancer Information Service toll-free at

1-800-4-CANCER

In Hawaii, on Oahu, call 524-1234 (call collect from neighboring islands). During daytime hours, Spanish-speaking CIS staff members are available to callers from the following areas: California, Florida, Georgia, Illinois, New Jersey (area code 201), New York, and Texas.

This Report was written by Patricia D. Lynch. Its scientific content has been approved by NCI scientists. Please direct questions or comments to the Research Reports Editor, National Cancer Institute, Office of Cancer Communications, Bethesda, Maryland 20892.